REMARKS

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Workgroup 1630, Art Unit 1634, and has been docketed to Primary Examiner Bradley L. Sisson.

Rejection under 35 U.S.C. 112

3. **Claim s 19, 56, 70, 78, 88, and 99** rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner contends as follows:

New Matter

4. **Claims 19, 56, 70, 78, 88, and 99** all refer to a collection of amino acid positions of SEQ ID NO. 11. Claim 19 is exemplary, and for convenience, is reproduced below.

> **19.(previously presented) The composition of claim 13, wherein the polymerase comprises *Taq* DNA polymerase 1 having a tag attached to an amino acid at a specific amino acid position of the *Taq* DNA polymerase 1, where the amino acid position is selected from the group consisting of 513-518,643, 647, 649 and 653-661 of SEQ. 10 No.11, where tbe tag comprises a fluorescent molecule.**

5. A review of the application finds that the application was originally filed with a Sequence Listing that contained 48 sequence listings, and had the following for SEQ ID NO. 11:

> **<210> 11**
> **<211> 36**
> **<212> DNA**
> **<213> Thermus aquaticus**
>
> **<220>**
> **<221> Mutation**
> **<222> (22)..(24)**
> **<223> Taq Pol I Mutation Complimentary Strand: AA. Site 652 glu to cys: antisense codon: ctc -> gca. 5' to 3' listing.**
>
> **<400> 11**
> **gcgc.atcagg gggtccacgg cgcaccgggg gacgcc**
> **36**

6. A review of the current Sequence Listing finds that SEQ ID NO. 11 is not some 832 amino acids in length. Further, a review of the original Sequence Listing fails to find where applicant had disclosed under any SEQ ID NO. a protein that was 832 amino acids in length.

7. A review of the file history fails to find where applicant contemplated, and properly incorporated by reference, the now disclosed amino acid sequence.

8. It is further noted that upon review of the disclosure, applicant had contemplated various mutants of Taq polymerase, and at no time was this specific amino acid sequence disclosed. In view of the apparent addition of this sequence to the disclosure, the specification and claims 19, 56, 70, 78, 88, and 99 are deemed to comprise new matter.

Applicants respectfully disagree with the Examiner. Examiner Smith required Applicants to add the fully *Taq* Polymerase I listing very early in the prosecution of this case, SEQ. ID NO. 11. So the sequencing listing to *Taq* sites are fully enabled. The *Taq* polymerase I sequence was contained in a document incorporated by reference: Eom *et al.*, 1996; Li *et al.*, 1998a; Li *et al.*, 1998b. The sequence was added on 03-11-2004 in the sequence listing filed that day. Applicants, therefore, respectfully request withdrawal of this section 112, first paragraph rejection.

9. **Claims 10, 17, and 18** have been construed in an particular way:

The Examiner contends as follows:

> Claims 10, 17, and 18 have been construed as encompassing a "polymerizing agent" that would serve to polymerize nucleotides, but also any other polymer, be it a cellulose, plastics, rubber, lipoproteins, etc. A review of the disclosure fails to find where applicant had contemplated these alternative embodiments and had provided such full, clear, and concise description of the compounds, and of the methods for making and using same, so as to reasonably suggest that applicant had possession of the full genus encompassed by the claims.
>
> 10. Attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:
>
> > It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.
> >
> > ***
> >
> > We are of the opinion that a genus containing such a large number of species cannot properly be identified by the mere recitation or reduction to practice of four or five of them. As was pointed out by the examiner, four species might be held to support a genus, if such genus is disclosed in clear language; but where those species must be relied on not only to illustrate the genus but to define what it is, the situation is otherwise.
>
> 11. Applicant is urged to consider narrowing the claims to those embodiments where the polymer is a nucleic acid and the "polymerizing agent" is a polymerase.

Applicants also respectfully disagree with the Examiner's interpretation of the term polymerizing agent. The term as set forth in the specification was intended to cover nucleotide, peptide and sugar biosynthesis, where the synthesis is template dependent, *i.e.*, stepwise based on a known template sequence. The terms is not meant to be for general polymerization, but it is not restricted to nucleotide polymerization using polymerase only. Peptide synthesis using tagged monomers (tRNAs or tagged amino acids) and tagged ribsomes or associated proteins are within the

broad context of the present application, as is saccharide synthesis where the synthesis is stepwise based on a known template.

However, in order to expedite the prosecution of this application, Applicants have amended the claims to change polymerizing agent to polymerase and monomer to nucleotide in the pending and newly added claims. Applicant expressly reserve the right to file applications directed to amino acid and saccharide synthesis.

Applicants therefore, respectfully request withdrawal this rejection.

13. **Claims 10, 16, 17, 18, 50, 64, 68, 71, 79, 89, 96, 97, 100, 105, and 106** stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner contends as follows:

> 14. Claims 10, 16, 17, 18, 50, 64, 68, 71, 79, 89, 96, 97, 100, 105, and 106 are indefinite with respect to just what constitutes the metes and bounds of a "polymerizing agent."
> 15. Claim 17 recites the limitation "the polymerase tag" in line 2. There is insufficient antecedent basis for this limitation in the claim.
> 16. Claim 55 recites the limitation "the polymerase tag" in line 2. There is insufficient antecedent basis for this limitation in the claim.
> 17. Claim 69 recites the limitation "the polymerase tag" in line 2. There is insufficient antecedent basis for this limitation in the claim.
> 18. Claim 77 recites the limitation "the polymerase tag" in line 2. There is insufficient antecedent basis for this limitation in the claim.
> 19. Claim 87 recites the limitation "the polymerase tag" in line 2. There is insufficient antecedent basis for this limitation in the claim.
> 20. Claim 98 recites the limitation "the polymerase tag" in line 2. There is insufficient antecedent basis for this limitation in the claim.
> 21. Claim 102 recites the limitation "the polymerase" in line 1. There is insufficient antecedent basis for this limitation in the claim.
> 22. Claim 103 recites the limitation "the polymerase" in line 1. There is insufficient antecedent basis for this limitation in the claim.
> 23. Claim 104 recites the limitation "the polymerase" in line 1. There is insufficient antecedent basis for this limitation in the claim.
> 24. Claim 107 is confusing in that claim 13 from which it depends recites a polymerase, yet claim 107 uses the indefinite article "a." Is the polymerase of claim 107 a different polymerase from that recited in claim 13, of is it the same?

Applicants have amended the claims to replace the term polymerizing agent with the term polymerase and the term monomer with the term nucleotide removing these 112, second paragraph issues. Applicants have also canceled claim 107 due to the change from polymerizing agent to

polymerase mooting this issue. Applicants therefore, respectfully request withdrawal this rejection.

Claim Rejections - 35 USC § 102/103

29. **Claims 10, 13, 17, and 18** stand rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent 6,982,146 B1 (Schneider et al.).

The Examiner contends as follows:

> 30. It is noted that while Schneider et al., was published 03 January 2006, it claims benefit of priority to provisional application 60/151,580, filed 30 August 1999. In comparison, the instant application claims benefit of priority to provisional application filed 07 July 2000. Accordingly, Schneider et al., qualifies as 102(e)-type art.
> 31. Schneider et al., disclose methods, and related compositions, for conducting sequencing reactions. As seen at column 5, the polymerase and nucleotides are both labeled, and that either can serve as a donor or acceptor of a signal, which can be fluorophores.
> 32. Schneider et al., column 9, teach explicitly of the application of fluorescence resonance energy transfer (FRET).
> 33. Schneider et al., column 10, teaches that "[o]ne of ordinary skill in the art can easily determine...which fluorophores will make suitable donor-acceptor FRET pairs.
> 34. Schneider et al., column 13, disclose a plethora of polymerizing agents.
> 35. Schneider et al., column 25, teach that the fluorophore can be linked directly or indirectly to the nucleotide.
> 36. Schneider et al., column 9, teach that the donor and acceptor fluorophores need to be within 10 to 100 Angstroms of one another for fluorescence resonance energy transfer to take place.
> 37. In view of the above remarks, and in the absence of convincing evidence to the contrary, claims 10, 13, 17, and 18 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent 6,982,146 B1 (Schneider et al.).

Schneider et al. does not teach or even suggest a sequencing composition including nucleotides bearing tags bonded to a part of the nucleotide that is released during nucleotide incorporation – non-persistent labeling – labeling that is not incorporated into the growing DNA sequence – in a FRET type sequencing strategy. "The nucleotides disclosed herein also include nucleotides containing modified bases, modified sugar moieties and modified phosphate backbones . . . " Schneider et al. at Col. 12, ll. 20-22. See also Schneider et al. at Col. 12, ll. 25-51.

The problem with base, sugar or backbone phosphate labeling is that the labels remain on the DNA strand after the nucleotide is incorporated. Schneider et al. recognized this problem, but gave little guidance on how to solve the problem. Schneider et al. did suggest: (1) using bulky linker to reduce FRET from previous base, (2) attaching a Dnase to the end of the polymerase to cleave

the nucleotide after incorporation or (3) using fluorescent molecules containing two attachment points. Schneider et al. at Col. 23 starting at line 51 to Col. 25 ending at line 67. Thus, the problems associated with the use of persistently labeled nucleotides would either require a second step to remove the labels or the labels would have to specifically designed to minimize FRET from previously incorporated nucleotides.

Regardless of the remedy, the Schneider et al. FRET methodology, like the Korlach et al. FRET methodology, suffered from the use of persistently labeled nucleotides. A deficiency not present in the methodology of this invention, where the sequencing information results from the detection of non-persistently labeled nucleotides before, during and/or after a nucleotide incorporation event. The use of non-persistently labeled nucleotides in a FRET methodology as set forth in certain of the claims of this invention greatly simplifies FRET detection by insuring that the FRET signal does not includes contributions from previously incorporated nucleotides; thus, the FRET signal is associated with a single nucleotide and not with an unknown mixture of nucleotide, which could so confuse the signal, that identification would be difficult in not impossible unless the other labels were deactivated or cleaved.

Moreover, because Schneider et al., like Korlach et al., disclosed FRET sequencing strategies using persistently labeled nucleotides (*i.e.*, nucleotides labeled on the base, sugar or backbone phosphate or labeled on the part of the nucleotide that remains after nucleotide incorporation) and labeled polymerases, teaching of Schneider et al., especially in light of th teaching of Korlach et al., teach strongly away from sequencing compositions using non-persistently labeled nucleotides (labeled on the part of the nucleotide released after nucleotide incorporation). **These two groups of extraordinary artisans did not disclose or even suggest the use non-persistently labeled nucleotides in a FRET sequencing strategy or a composition designed for accomplishing the strategy.** Thus, if two groups of extraordinary artisans did not recognize a sequencing strategy using non-persistently labeled nucleotides and its corresponding composition, how can the Patent Office now contend that an ordinary artisan would have recognized such a strategy and its corresponding composition.

Furthermore, Schneider et al. included absolutely no teaching or even a suggestion to use non-persistently labeled nucleotides in an sequencing strategy or its corresponding composition. Non-persistently labeled nucleotides generate DNA sequences that do no include labels, and there is, therefore, no potential for interference from labels on previously incorporated nucleotides. This sequencing strategy is simply not disclosed or even suggested by Schneider et al. This sequencing

strategy not only reduces interference due to labels on previously incorporated nucleotides, but in a FRET strategy (FRET is not the only detection contemplated by the claims of this invention), the strategy permits the detection of a FRET signal due to a single labeled nucleotide in close proximity the label on the polymerase free of interference with labels on previously incorporated nucleotides.

Because Schneider et al. did not disclose sequencing strategies using nucleotide bearing labels on the part of the nucleotide that is releases during incorporation of the nucleotide into the growing DNA chain, Schneider et al. cannot anticipate Claims 10, 13, 17, and 18.

Moreover, because Schneider et al. does not even suggest sequencing using nucleotide bearing labels on the part of the nucleotide that is releases upon incorporation of the nucleotide, Schneider et al. cannot even render obvious Claims 10, 13, 17, and 18.

Further more, two groups of extraordinary artisans (Schneider et al. and Korlach et al.) did not recognize such sequencing strategies, therefore, an ordinary artisan clearly would not.

Applicants therefore, respectfully request withdrawal this rejection.

38. **Claims 16, 19, 50-56, 64-74, 76-92, 94-100, and 102-107** stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,982,146 B1 (Schneider et al.) in view of US Patent 7,037,687 B2 (Williams et al.) and US Patent 5,849,478 (Cashman).

The Examiner contends as follows:

> 39. It is noted that while Schneider et al., was published 03 January 2006, it claims benefit of priority to provisional application 60/151,580, filed 30 August 1999. In comparison, the instant application claims benefit of priority to provisional application filed 07 July 2000. Accordingly, Schneider et al., qualifies as 102(e)-type art.
> 40. Schneider et al., disclose methods, and related compositions, for conducting sequencing reactions. As seen at column 5, the polymerase and nucleotides are both labeled, and that either can serve as a donor or acceptor of a signal, which can be fluorophores.
> 41. Schneider et al., column 9, teach explicitly of the application of fluorescence resonance energy transfer (FRET).
> 42. Schneider et al., column 10, teaches that "[o]ne of ordinary skill in the art can easily determine...which fluorophores will make suitable donor-acceptor FRET pairs.
> 43. Schneider et al., column 13, disclose a plethora of polymerizing agents, which include DNA polymerase I, Taq polymerase, reverse transcriptase, and RNA polymerase.
> 44. Schneider et al., column 25, teach that the fluorophore can be linked directly or indirectly to the nucleotide.
> 45. Schneider et al., column 9, teach that the donor and acceptor fluorophores need to be within 10 to 100 Angstroms of one another for fluorescence resonance energy transfer to take place.
> 46. While Schneider et al. disclose numerous polymerases, they do not teach specifically if the polymerases lack exonuclease activity.
> 47. Williams et al., column 4, teach that their method utilizes polymerases that are deficient in exonuclease activity.
> 48. Williams et al., column 7, disclose polymerases that are useful in such a procedure. As seen therein, one such polymerizing agent is *Taq* polymerase as well as T7 DNA polymerase, Klenow polymerase, reverse transcriptase, etc.

49. Williams et al., column 12, bridging to column 13, disclose using fluorescentlylabeled nucleotides, and their being incorporated by the aforementioned polymerases.

50. Neither Schneider et al., nor Williams et al., have been found to disclose using nucleotide where the fluorescent label is attached to a terminal phosphate.

51. Cashman, column 12, teach explicitly of devising kits that comprise not only any of a variety of polymerases, but also nucleotides that bear a fluorescent label attached to a terminal phosphate.

52. It would have been obvious to one of ordinary ski in the art at the time the invention was made to have combined the compositions of Cashman with that of Williams et al., and Schneider et al., as such would have allowed the ordinary artisan to combined labeled polymerases with labeled nucleotides wherein the labels can be a member of a FRET pair, As the prior art teaches explicitly of using both these polymerases with terminal phosphate labeled nucleotides.

53. Neither Schneider et al., Williams, nor Cushman have been found to teach the specific amino acids positions of *Taq* polymerase recited in claims 19, 56, 70, 78, 88, and 99. The selection of which amino acid of *Taq* polymerase to be labeled is not deemed to constitute a patentable distinction as Schneider et al., column 9, teach that the donor and acceptor fluorophores need to be within 10 to 100 Angstroms of one another for fluorescence resonance energy transfer to take place. With Cashman teaching the use of terminal-phosphate labeled nucleotide, it would be a matter of routine experimentation and optimization to identify those amino acids that would result in the FRET pair being within the prescribed distance.

54. It is well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. In support of this position, attention is directed to the decision in *In re Aller, Lacey, and Hall,* 105 USPQ 233 (CCPA 1955):

> Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In re Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added)

55. Attention is directed to the decision in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007)

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

56. For the above reasons, and in the absence of convincing evidence to the contrary, claims 16, 19, 50-56, 64-74, 76-92, 94-100, and 102-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,982,146 B1 (Schneider et al.) in view of US Patent 7,037,687 B2 (Williams et al.) and US Patent 5,849,478 (Cashman).

Applicants reassert their arguments regarding Schneider et al. here. The inclusion of Williams et al. and Cushman does nothing to alleviate the deficiencies in Schneider et al. Schneider et al. did not disclose the use of nucleotides bearing non-persistent labels in sequencing strategies including FRET strategies.

Williams et al. relates to a step-wise sequencing strategy, where each label must be removed after each nucleotide is incorporated. Thus, Williams et al. did not disclose or even suggest a sequencing strategy where a sequence of incorporation events are determined as a sequence of

nucleotide is incorporated without the need for removing the label.

Cushman did disclose gamma labeled nucleotides, but in an immunoassay method and kit, where the immunoassay relates to determining the amount of fluorophore in the solution after the assay has been performed. Cushman did not look at each individual incorporation event and did not disclose a sequencing method where at least one of the tags has a fluorescence property that is detectable before, during and/or after each of a sequence of nucleotide incorporations due to an interaction between the polymerase and the nucleotide.

Moreover, Williams et al. and Cushman did not disclose or even suggest a real-time sequencing method, where each incorporating nucleotide is detected and identified during its incorporation.

Thus, the combination of Schneider et al., Williams et al. and Cushman does not render Claims 16, 19, 50-56, 64-74, 76-92, 94-100, and 102-107 and new claims 108-117 obvious, because the combination does not overcome the basic deficiencies in Schneider et al. as it relates to sequencing using a tagged polymerase and nucleotide type bearing labels on the part of the nucleotide released during incorporation, where at least one of the tags has a fluorescence property that is detectable before, during and/or after each of a sequence of nucleotide incorporations due to an interaction between the polymerase and the nucleotide and where the polymerase lacks the ability to remove a previously incorporated nucleotide. Schneider et al. and other extraordinary artisans (Korlach et al.) did not recognize the sequencing strategies of this invention; William et al. did not relate to continuous, real-time sequencing strategies; Cushman did not relate to sequencing at all, but to assays based on bulk incorporation of labeled nucleotides albeit gamma labeled nucleotide. Ordinary artisan, therefore, would not recognize the present invention as obvious in that Schneider et al. and Korlach et al. did not recognize this strategy either.

Because the combination does not even suggest the sequencing compositions of this invention as extraordinary artisan did not recognize them, the combination cannot render Claims 16, 19, 50-56, 64-74, 76-92, 94-100, and 102-107 and new claims 108-117 obvious. Applicants therefore, respectfully request withdrawal this rejection.

Having fully responded to the Examiner's Non-Final Office Action, Applicant respectfully urges that is application be passed onto allowance.

If it would be of assistance in resolving any issues in this application, the Examiner is kindly invited to contact applicant's attorney Robert W. Strozier at 713.977.7000

The Commissioner is authorized to charge or credit deposit account 501518 for any fees due or any overpayments, respectively.

If the Examiner requires additional information, then Applicants request that the Examiner contact their Attorney, Robert W. Strozier, at 713-977-7000.

Respectfully submitted,

Date: **10 March 2008**

Robert W. Strozier
Reg. No. 34,024